APPENDIX I

Attorney's Docket No.: 705152-2001
Application No.: 10/589,751

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Francese GIANCARLO *et al.*	)	Group Art Unit: 1614
	)	
Application Serial No.: 10/589,751	)	Examiner: Savitha M. RAO
	)	
Filed: August 17, 2006	)	Confirmation No.: 9535
	)	
For: A PROCESS FOR THE PREPARATION OF CRYSTALLINE (6RS)-N(5)-FORMYL-5,6,7,8-TETRAHYDROFOLIC ACID	)	

DECLARATION UNDER 37 CFR.1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Fabrizio Marazza, declare as follows:

1. The diastereoisomeric purity of (6S)-Folinic Acid and of the (6S)-Sodium Folinate or (6S)-Potassium Folinate solution derived there from is determined only by the diastereoisomeric purity of the starting material (6S)-Calcium Folinate. At the same time the diastereoisomeric purity of (6S)-Calcium Folinate is determined only by the diastereoisomeric purity of the precursor (6S)-5,6,7,8-Tetrahydrofolic Acid. The isomeric purity as such does not change during this transformations, i.e., formylation, of (6S)-5,6,7,8-Tetrahydrofolic Acid and salt formation of the obtained (6S)-Folinic Acid.
2. In example 2 of the US Patent Application No. 10/589,751 it is stated that (6S)Calcium Folinate is "prepared according to EP 600 460 and NO 172 492". EP 600 460

corresponds to U.S. Patent No. 5,489,684. U.S. Patent No. 5,489,684 discloses in claim 1 that the (6S)-5,6,7,8-Tetrahydrofolic Acid has a diastereoisomeric purity of "at least 75%". In Example 1, at column 4, line 13 of U.S. Patent No. 5,489,684, the diastereoisomeric purity is described as "80.5%". In Example 2, at column 4, line 29 of U.S. Patent No. 5,489,684 the diastereoisomeric purity is described as "93%". Accordingly, the diastereoisomeric purity of the (6S)-Sodium Folinate or (6S)-Potassium Folinate solution prepared according to EP 600 460 and NO 172 492 will be at least 75%.

3. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code.

F. Marazza

Fabrizio Marazza, PhD
IP manager
Cerbios-Pharma SA
Barbengo,

August 24, 2010
Date

APPENDIX II

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DECLARATION UNDER 37 CFR.1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Fabrizio Marazza, declare as follows:

1. During the period prior to filing of Swiss Patent Application No. 00285/04 (having the priority date of February 20,2004), from which subject United States application was derived, I was the supervisor (R&D director) of both co-inventors of the subject application, i.e., Dr. G. Francese and M. Morosoli. Dr. G. Francese left the company few years ago. M. Morosoli is a technician still active at Cerbios-Pharma SA.
2. Several experiments were performed in order to find a suitable method of preparing (6S)-folinic acid. As stated in the US Application No. 10/589,751, several attempts to reproduce Example 6 of EP 0 293 751 (by Müller et al.), corresponding to U.S. Patent No. 6,160,116, always led to an untreatable, rubber like product.

3. A copy of the description of one of the experiments mentioned under point 2 is enclosed (a lab-journal page in Italian language). An English translation of this text is also enclosed.

4. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code.

F. Marazza

Fabrizio Marazza, PhD
IP manager
Cerbios-Pharma SA
Barbengo,

August 24, 2010
Date

Solubilità (6S)-GF in H_2O a 55°-60°C

HPLC WS 1.3 ⇒ 22063.4 counts

Scaldato 100 ml H_2O a 55°-58°C Add (6S)-GF CJ0834 a portion ~4.2 g HPLC (dil 1:20) ⇒ C = 3.7%

Prova precipitazione Acido Folinico direttamente dalla sol di (6S)-GF

1. (6S)-GF (CJ0834) : 11.5 g (= 10 g secchi
2. H_2O demi : 300 ml
3. HCl 0.5 N

Sciolto 1 in 2 a 58°C pH 7.51 Raffreddato a 10°C → sol limpida pH 8.23 Add HCl 0.5 N in 30' fino a pH 3.0 T = 9.7°C
Stabilizzato con HCl 0.5 N per 30' poi 1 ora a 10°C
Filt (D2) e lavato 1x 50 ml H_2O senza risospendere → molto igroscopico
Solido ripreso in Acetone → gomma!

Analisi nel Quaderno verde N° 12

Tancredi Mariel 15.12.03 F. Marazza 17.12.03

cerbios

English translation of the lab-journal page no. 2246 (Notebook No. 23) / December 15, 2003
by Moreno Morosoli
(The relevant description starts at line 5)

Test of direct precipitation of Folinic Acid from a solution of (6S)-CaF

1. (6S)-CaF (CJ0834): 11.5 g (= 10 g dry)
2. H_2O (seralpure quality): 300 ml
3. HCl 0.5N

1. was dissolved in 2. at 58°C, pH 7.51. Solution was cooled to 10°C resulting in a clear solution., pH=8.23 . During 30 min. under stirring 3. was added reaching a pH value of 3.0 (T=9.7°C) . The mixture was stirred further during 30 min. addiing 0.5 N HCl to keep the pH value at 3.0 and then the suspension was stirred for another hr (T=10°C). Filtration (D2) and washing with 50 ml of H_2O gave an hygroscopic sticky solid. A tentative resuspension of this solid in acetone resulted in a rubberlike untreatable product.

"analysis" in folder No. 12

Translated by F.Marazza / July 29, 2010

F. Marazza